REMARKS

This Response is to the Office Action mailed February 6, 2006. Claims 1 to 4 and 6 to 9 are pending and are under consideration.

Regarding the Previously Filed Sequence Listing

The Examiner has requested a statement requesting entry of the Substitute paper and computer readable copies of the Sequence Listing filed October 3, 2005. Accordingly, Applicants respectfully request entry of the Substitute paper and computer readable copies of the Sequence Listing filed October 3, 2005.

Regarding Skulimowski et al. (Method Mol. Genet. 7:3 (1995))

Applicants note that the Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) reference was previously cited in the Office Action mailed December 5, 2000, under 35 U.S.C. §103(a) in combination with numerous other references. Applicants submitted a Response and accompanying Declaration under 37 C.F.R. §1.131 on June 5, 2001 that included a reference to Skulimowski *et al.* Applicants respectfully submit that the reference to Skulimowski *et al.* in the Declaration under 37 C.F.R. §1.131 and applicable remarks in the Response were inadvertent and without deceptive intent. Applicants note that Skulimowski *et al.* has been cited anew in the Office Action mailed February 2, 2006. Accordingly, the Patent Office has recognized the inadvertent reference to Skulimowski *et al.* in the Declaration under 37 C.F.R. §1.131 and applicable remarks in the Response and, therefore, the inadvertent reference was without harm.

I. REJECTIONS UNDER 35 U.S.C. §103(a)

The rejection of claims 1 and 6 to 9 under 35 U.S.C. §103(a), as allegedly unpatentable over Smith *et al.* (Nat Genet. 5:397 (1993)), in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) is respectfully traversed. Allegedly, Smith *et al.* "teaches a virus to be used for delivering a gene encoding Factor IX into cells in vivo for gene therapy, which virus comprises a promoter/regulatory sequence, an isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions....and an SV40 early polyadenylation site" but "does not teach an AAV vector comprising at least two AAV inverted terminal repeats." Allegedly, "Skulimowski *et al.* teaches a composition comprising an AAV vector comprising two AAV inverted terminal

repeats" and that "it is able to insert its genome locus-specifically into human chromosomes." Allegedly, a "motivation to combine....is found in the nature of the problem to be solved by the composition of Smith *et al.*.....and the limitations of adenoviral vectors....," namely, allegedly that "Smith *et al.* found that expression of Factor IX was transient, which Smith *et al.* teaches was likely due, at least in part, to a loss of vector DNA," which, allegedly, "the skilled artisan would have been motivated to substitute the AAV vector of Skulimowski *et al.* for the adenovirus vector of Smith *et al.*" [See, Office Action, pages 4-6]

Claims 1 and 6 to 9 would not have been obvious in view of Smith *et al.* (Nat Genet. 5:397 (1993)) or Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) alone, or in combination, at the time of the invention. In order for a rejection to be proper under 35 U.S.C. §103(a), *inter alia*, there must have been 1) a suggestion or motivation to combine the references at the time of the invention; 2) the combination of references must teach or suggest each and every element of the claimed invention; and 3) there must have been a reasonable expectation of success at the time of the invention. Both the teaching or suggestion to make the claimed combination *and* reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988). Even where the combination of references teaches every element of the claimed invention, without a motivation to combine, a rejection based on a prima facie case of obviousness is improper. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998); *see also*, *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). In addition, a prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Here, *inter alia*, there is 1) neither the requisite suggestion or motivation to combine the cited references, 2) nor a reasonable expectation of success, at the time of the invention. Furthermore, evidence that one skilled in the art would not have combined the cited references at the time of the invention is present in Smith *et al.*, and is also submitted herewith as Exhibits D and E, a Review article by Anderson, W.F. (Nature 392:25 (1998)) and an Editorial by Muzyczka, N. (J. Clin. Invest. 94:1351 (1994)), respectively.

Turning to Smith *et al.*, this publication reports studies with adenovirus vector mediated expression of human Factor IX in mice. The authors report that expression was transient, which "may have been due, in part, to attenuation of vector expression." (page 400, second column, last paragraph) The authors state that "since adenoviral vector mediated gene expression is transient, a long term clinical protocol for haemophilia B will require repeated vector administrations." The authors report that no human Factor IX was detected in the plasma after a second injection, stating that "it will be necessary to develop vectors and delivery procedures which are less immunogenic" and that "eventually it will be necessary to devise a strategy to administer vector to patients who have neutralizing antibodies from a prior infection with wild type adenovirus." (page 401, first column, first full paragraph) Thus, in view of the foregoing, it is clear that Smith *et al.* at most teach or suggest modifying adenovirus vectors or adenovirus vector administration protocols, or using a retrovirus vector, not completely abandoning adenovirus vectors for a completely different vector such as AAV vector. Notably, although Smith *et al.* mentions a study with a retroviral vector in a *Note added in proof*- there is no mention whatsoever of an AAV vector. Consequently, it cannot fairly be said that Smith *et al.* teaches or suggests, or provides any motivation, to substitute an adenovirus vector with an AAV vector.

To corroborate that the skilled artisan would not have been motivated to substitute an adenovirus vector with an AAV vector, Applicants respectfully direct the Examiner's attention to Exhibit D, submitted herewith (Anderson, W.F., Nature 392:25 (1998)). In brief, the author discusses adenoviral vectors pointing out that they are "the DNA virus most widely used for in situ gene transfer," and that "adenoviral vectors have several positive attributes: they are large and can potentially hold large DNA inserts....they are human viruses and are able to transduce a large number of different cells types at a very high efficiency....they can transduce non-dividing cells; and they can be produced at very high titres in culture." (page 27, second column, last paragraph) The author also mentions certain drawbacks of adenoviral vectors, such as those with E1 and E3 deleted eliciting strong immune responses, but discusses additional adenoviral gene deletions such as "E2a and/or E4," and "gutless" vectors in order to reduce immune responses, as well as repeated administrations of these vectors. (page 28, first column) The authors also discuss using "transient immunosuppression of the patient to allow repeated administration of vectors" and "to blockade costimulatory interactions required for an immune response to

antigen." (page 28, first column) In terms of AAV vectors, the author mentions genome integration, but the discussion of drawbacks is far lengthier, including, integration specificity, requirement of high multiplicity of infection, the small size of the AAV genome, and that production of viral particles is labor intensive and the lack of efficient packaging cells. (page 28, first column, last paragraph, through second column, first full paragraph) Thus, in view of Smith *et al.* and Exhibit D *in toto*, the skilled artisan would have at most been motivated to employ alternative adenovirus vectors, such as E2a and/or E4 deleted or gutless adenovirus vectors, or an immune-suppressive therapy.

Even if for the sake of argument the skilled artisan were to completely abandon the adenovirus vector of Smith *et al.* and try another vector, Smith *et al.* at most mention retrovirus. Consequently, the skilled artisan at most would have been motivated to substitute the adenovirus vector with a retrovirus vector not an AAV vector.

Furthermore, it was uncertain at the time of the invention whether an AAV vector could integrate into the cellular chromosome and therefore, would solve the problem of transient expression. Because it was unknown if an AAV vector could integrate into the cellular chromosome at the time of the invention, Skulimowski *et al.* does not provide the skilled artisan with a motivation to substitute the adenovirus vector of Smith *et al.* with an AAV vector for the purpose of solving the problem of transient expression.

In support of Applicant's position, Skulimowski *et al.* describe adeno-associated vectors for potential human gene therapy (see Introduction). Although Skulimowski *et al.* state that wild-type AAV integrates into human chromosome 19, Skulimowski *et al.* also state that "the role of vector integration *in vivo* remains to be evaluated." (page 10, Conclusion; underlining added). Thus, Skulimowski *et al.* teach that it was uncertain whether an AAV vector could integrate into the cellular chromosome.

Further in this regard, the Examiner's attention is respectfully directed to Exhibit E submitted herewith (Muzyczka, N., J. Clin. Invest. 94:1351 (1994)). In brief, the author of Exhibit E discusses several challenges associated with AAV vectors. One such challenge relates to the "intriguing property of AAV, namely, the wild-type genome integrates specifically into human chromosome 19." The author notes that "(w)hether this property can be retained in the recombinant vectors remains an open question." (Exhibit E, page 1351, first column, first paragraph, emphasis added.) In terms of this open question, the author continues by stating that

"no one has shown that transduction in primary cells is permanent, that is, that the AAV vector has, in fact integrated. Indeed, there is almost no direct evidence that AAV vectors will integrate into primary cells." (Exhibit E, page 1351, second column, last paragraph) Thus, in view of the uncertainty in the art at the time of the invention as to whether or not AAV vectors could integrate into the cellular genome, the skilled artisan would not have had a reasonable expectation that an AAV vector could "solve the problem" of transient expression. In view of the fact that the skilled artisan would not have had a reasonable expectation that an AAV vector would solve the problem of transient expression, the skilled artisan would not have been motivated to substitute the adenovirus vector with AAV vector of Skulimowski *et al.* for the purpose of solving the problem of transient expression. In sum, the uncertainty as to whether AAV vector integrates into the cellular genome clearly contradicts the assertion that the skilled artisan would have been motivated to use the AAV vector of Skulimowski *et al.* for the purpose of solving the problem of transient expression.

In sum, neither Smith *et al.* nor Skulimowski *et al.* teach or suggest substituting an adenovirus vector with an AAV vector in order to produce the pharmaceutical compositions of claims 1 and 6 to 9. They do not provide the requisite motivation to substitute an adenovirus vector with an AAV vector at the time of the invention in order to produce the pharmaceutical compositions of claims 1 and 6 to 9. Specifically, in view of the uncertainty of AAV vector integrating into the cellular genome, claims 1 and 6 to 9 would not have been obvious in view of Smith *et al.* or Skulimowski *et al.* alone, or in combination, at the time of the invention. Consequently, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) over Smith *et al.* (Nat Genet. 5:397 (1993)) in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) be withdrawn.

The rejection of claims 1 and 6 to 9 under 35 U.S.C. §103(a), as allegedly unpatentable over Miyanohara *et al.* (New Biol. 4:238 (1992)), in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) is respectfully traversed. Allegedly, Miyanohara *et al.* "teaches a virus to be used for delivering a gene encoding Factor IX into cells *in vivo* for gene therapy, which virus comprises a promoter/regulatory sequence, an isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions....and an SV40 early polyadenylation site" but "does not teach an AAV vector comprising at least two AAV inverted terminal repeats."

Allegedly, "Skulimowski *et al.* teaches a composition comprising an AAV vector comprising two AAV inverted terminal repeats" and that "it is able to insert its genome locus-specifically into human chromosomes." Allegedly, a "motivation to combine....is found in the nature of the problem to be solved by the composition of Miyanohara *et al.*.....and the limitations of HSV vectors....," namely, allegedly that "Miyanohara *et al.* found that expression of Factor IX was transient....and that cytotoxicity is a problem associated with the use of HSV vectors," which, allegedly, "the skilled artisan would be motivated to substitute the AAV vector of Skulimowski *et al.* for the HSV vector of Miyanohara *et al.*" [see, Office Action, pages 7-9]

Claims 1 and 6 to 9 would not have been obvious in view of Miyanohara *et al.* (New Biol. 4:238 (1992)) or Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) alone, or in combination, at the time of the invention. An artisan would not have been motivated to substitute an AAV vector for an HSV vector because Skulimowski *et al.* does not teach or suggest any information about the toxicity, or lack thereof, of a recombinant AAV vector delivered *in vivo*. Moreover, an artisan would have no reasonable expectation of success in substituting a recombinant AAV vector for an HSV vector based on Skulimowski *et al.* because Skulimowski *et al.* fail to teach or suggest any information regarding recombinant AAV toxicity *in vivo*. Rather, Skulimowski *et al.* at most makes general statements regarding the fact that wild-type AAV infection has never caused human disease.

Turning to Miyanohara *et al.*, this publication reports studies with HSV vector mediated expression of canine Factor IX in mice. The authors reported two problems, namely cytotoxicity and gene expression shutdown (page 243, second column). In terms of cytotoxicity, the authors state that "with further vector manipulation the problem of cytotoxicity is potentially solvable, and noncytopathic herpes vectors are therefore likely to become available in the not too distant future." In terms of expression, the authors state that "factors that can influence transgene expression in HSV-1 vectors have been shown to include the mutant virus background, the genomic location of the transgene insert, and the infected cell type...."understanding of the influence of these parameters on the activity of different promoters driving transgene expression in the HSV-1 genome may aid the design of vectors that stably produce higher levels of transgene product." (page 243, second column) Notably absent from Miyanohara *et al.* is any teaching or suggestion to abandon the HSV vector for another vector, let alone an AAV vector.

In fact, Miyanohara *et al.* conclude that "it is now clear that the application of HSV-1 vectors for gene transfer should be expanded to other cells and organs in addition to neurons, both in vitro and in vivo." (page 244, first column, last paragraph) Consequently, in view of the foregoing, it is clear that Miyanohara *et al.* at most teach or suggest improving HSV vectors and expanding the use of HSV vectors to other cells and organs, not completely abandoning HSV vectors for a different class of vectors, let alone an AAV vector. Consequently, it cannot fairly be said that Miyanohara *et al.* teach or suggest, or provide any motivation, to substitute an HSV vector with an AAV vector.

Furthermore, in terms of the assertion that a recombinant AAV vector would solve the problem of "HSV cytotoxicity," there is no corroborating data or other evidence provided to substantiate this assertion. In this regard, Miyanohara *et al.* states that HSV cytotoxicity "seem to involve" expression of some HSV genes and that "with further vector manipulation the problem of cytotoxicity is potentially solvable," indicating that the causes of HSV cytotoxicity are not fully understood. (page 243, second column) Turning to Skulimowski *et al.*, the authors state that wild type AAV has "never been identified as a causative agent of human disease". However, Skulimowski *et al.* is silent with respect to the toxicity profile of a recombinant AAV vector, which Applicants respectfully assert is the relevant issue because a wild-type AAV infection is significantly different than the bolus delivery of a recombinant AAV vector in vivo.

Absent an understanding of the causes of HSV cytotoxicity and absent any teaching regarding the toxicity of recombinant AAV vectors *in vivo*, the skilled artisan at the time of the invention would not have been motivated to substitute an AAV vector for an HSV vector. Moreover, an artisan would not have had a reasonable expectation of success in substituting a recombinant AAV vector for an HSV vector based on Skulimowski *et al.* due to the lack of data regarding recombinant AAV toxicity.

Even if for the sake of argument the skilled artisan were to completely abandon the HSV vector of Miyanohara *et al.* and try another vector, Miyanohara *et al.* fail to mention any other virus vector, let alone an AAV vector. Furthermore, as discussed above and corroborated by Skulimowski *et al.* and Exhibit E, it was unknown at the time of the invention whether an AAV vector could integrate into the cellular chromosome. Because it was unknown if an AAV vector could integrate into the cellular chromosome at the time of the invention, Skulimowski *et al.*

would not have provided the skilled artisan with a motivation to substitute the HSV vector with an AAV vector for the purpose of solving the problem of transient expression.

In sum, neither Miyanohara *et al.* nor Skulimowski *et al.* teach or suggest substituting an HSV vector with an AAV vector in order to produce the pharmaceutical compositions of claims 1 and 6 to 9. Furthermore, neither Miyanohara *et al.* nor Skulimowski *et al.* provide the requisite motivation or expectation of success to substitute an HSV vector with an AAV vector, particularly in view of 1) the uncertainty as to whether AAV vector integrates into the cellular genome; and 2) the absence of information in the cited references regarding the toxicity of recombinant AAV vectors. Thus, claims 1 and 6 to 9 would not have been obvious in view of Miyanohara *et al.* or Skulimowski *et al.* alone, or in combination, at the time of the invention. Consequently, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) over Miyanohara *et al.* (New Biol. 4:238 (1992)) in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) be withdrawn.

The rejection of claims 1 to 3 under 35 U.S.C. §103(a), as allegedly unpatentable over Smith *et al.* (Nat Genet. 5:397 (1993)) in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) or Miyanohara *et al.* (New Biol. 4:238 (1992)) in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) and further in view of Kurachi *et al.* (J. Biol. Chem. 270:5276 (1995)) is respectfully traversed. Each of Smith *et al.* in view of Skulimowski *et al.* and Miyanohara *et al.* in view of Skulimowski *et al.* have been discussed The Patent Office acknowledges that neither Smith *et al.* nor Miyanohara *et al.* teach that Factor IX expression cassette should comprise a portion of intron 1. Allegedly, Kurachi *et al.* describe inclusion of portions of Factor IX intron 1 in Factor IX expression cassettes.

As discussed above, claims 1 and 6 to 9 would not have been obvious in view of either of Smith *et al.* and Skulimowski *et al.* alone, or in combination, or Miyanohara *et al.* and Skulimowski *et al.* alone, or in combination. The addition of Kurachi *et al.* does not provide that which is missing from any of Smith *et al.*, Skulimowski *et al.* and Miyanohara *et al.* Thus, claims 1 to 3 would not have been obvious in view of any of Smith *et al.*, Skulimowski *et al.*, Miyanohara *et al.* and Kurachi *et al.* alone, or in any combination.

In particular, among other things, neither Smith *et al.* nor Miyanohara *et al.* teach or suggest abandoning adenovirus vectors or HSV vectors for another vector, let alone an AAV vector. At most, Smith *et al.* and Miyanohara *et al.* teach or suggest improving adenovirus vectors or HSV vectors, devising new administration protocols with adenovirus vectors or HSV vectors or expanding the use of HSV vectors to other cells and organs. Notably absent from both of Smith *et al.* and Miyanohara *et al.* is any mention whatsoever of AAV vector. Consequently, it cannot fairly be said that either Smith *et al.* or Miyanohara *et al.* teach or suggest, or provide any motivation, to substitute an adenovirus vector or an HSV vector with an AAV vector.

In terms of the assertion that AAV vector would solve the problem of adenovirus vector or HSV vector transient expression, as discussed above and corroborated by Skulimowski *et al.* and Exhibit E, it was unknown at the time of the invention whether AAV vector could integrate into the cellular chromosome. Because it was unknown if an AAV vector could integrate into the cellular chromosome at the time of the invention Skulimowski *et al.* does not provide the skilled artisan with a motivation to substitute the adenovirus vector or HSV vector with an AAV vector for the purpose of solving the problem of transient expression.

In terms of AAV vector solving the problem of HSV cytotoxicity, as discussed above the cited references do not provide evidence regarding the toxicity of recombinant AAV vectors. Furthermore, the causes of HSV cytotoxicity were not understood. Absent a teaching or suggestion regarding the toxicity of AAV vectors *in vivo*, or an understanding of the causes of HSV cytotoxicity, the skilled artisan at the time of the invention would not view AAV vectors as solving the problem of HSV cytotoxicity.

In sum, neither Smith *et al.*, Miyanohara *et al.*, Skulimowski *et al.* nor Kurachi *et al.* alone, or in any combination, teach or suggest substituting an adenovirus vector or HSV vector with an AAV vector in order to produce the pharmaceutical compositions of claims 1 to 3. Furthermore, neither Smith *et al.*, Miyanohara *et al.*, Skulimowski *et al.* nor Kurachi *et al.* alone, or in any combination, provide the requisite motivation or reasonable expectation of success to substitute an adenovirus vector or HSV vector with an AAV vector at the time of the invention in order to produce the pharmaceutical compositions of claims 1 to 3, particularly in view of the uncertainty as to whether AAV vector integrates into the cellular genome. Consequently, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) over Smith *et al.* (Nat Genet. 5:397 (1993)) in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) or

Miyanohara *et al.* (New Biol. 4:238 (1992)) in view of Skulimowski *et al.* (Method Mol. Genet. 7:3 (1995)) and further in view of Kurachi *et al.* (J. Biol. Chem. 270:5276 (1995)) be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 4 and 6 to 9 clearly and patentably define the invention, respectfully request that the Examiner reconsider the ground set forth in the Office Action, and respectfully request allowance of the claims now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any fees associated with the submission of this paper to Deposit Account Number 03-3975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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